

Gordh TE, Stubhaug A, et al. Gabapentin in traumatic nerve injury pain: A randomized, double-blind, placebo-controlled, cross-over, multi-center study. Pain 2008;138:255-266.

Design: Randomized clinical trial

Population/sample size/setting:

- 120 patients (64 women, 56 men, mean age 49) treated for traumatic nerve injury pain at 9 centers in 4 Scandinavian countries
- Eligibility criteria were peripheral nerve injury caused by surgery or trauma at least 6 months duration, with pain intensity at least 30 on a 0-100 VAS, with hyper- or hypo-phenomena in sensibility tests in the distribution of the injured nerve
- Exclusion criteria were pregnancy, previous treatment with gabapentin, serum creatinine >2.5 upper normal limit, other pain that could confound the evaluation of the nerve injury pain, alcohol or drug abuse in past 3 years

Main outcome measures:

- There was a 2 week run-in period, during which 39 of 159 originally screened participants were excluded from randomization for not meeting entry criteria
- The randomized patients were treated for 5 weeks with either gabapentin or placebo, followed by a 3 week washout period when neither was taken, followed by 5 weeks when the patients switched to the opposite treatment
- 120 patients were randomized to either gabapentin-placebo (GP, n=61), or to placebo-gabapentin (PG, n=59); the maximum gabapentin dose was 2400 mg
- Primary outcome variable was mean pain intensity based on the last 14 of twice-daily VAS recordings for the run-in, first treatment, washout, and second treatment periods; at least 9 VAS recordings were required for measurement
- Response to treatment was defined as (1) at least 50% reduction in VAS, (2) at least 30% reduction in VAS, (3) marked relief of pain, or (4) moderate pain relief as judged by patient
- Several secondary measures were taken, including sleep, SF-36 quality of life, Clinical (CGIC) and Patient (PGIC) Global Impression of Change
- Blood was drawn for gabapentin levels at all visits in the morning before the morning dose of the study drug
- Pain VAS changed in both the GP and PG groups during the first period of treatment, by approximately equal amounts (7.2 and 6.9 points respectively)
- During the washout period, pain VAS increased in both groups by about 5 points; no carryover effect was observed
- Pain VAS in the second period decreased by a mean of 0.5 points in the GP group and by 5.1 points in the PG group; however, the analysis of covariance (ANCOVA) which adjusted for baseline pain VAS did not show a difference between the treatments

- Pain relief scored on a scale of marked/moderate/some/none did show more patients with marked/moderate relief during gabapentin (n=31) than during placebo (n=14)
- A 50% reduction in pain was reported more often during gabapentin (n=22) than during placebo (n=8)
- More than half of patients (54/98) had no pain relief with gabapentin, and only 1/3 of gabapentin patients had moderate relief or better
- Some secondary measures showed statistically significant superiority of gabapentin over placebo: sleep interference, SF-36 quality of life, CGIC, and PGIC
- Adverse effects such as dizziness (32.5%), tiredness (25.8%), and confusion (13.3%) were reported more frequently during gabapentin treatment periods than during placebo (7.5% , 14.2%, and 1.7% respectively)

Authors' conclusions:

- Gabapentin was not superior to placebo on the primary outcome measure of VAS adjusted for baseline pain intensity
- However, gabapentin was superior to placebo on several secondary measures, including the numbers of patients with moderate or marked pain relief and SF-36 quality of life
- The discrepancy may be due to the VAS not being an optimal outcome measure, when it has to be recorded twice per day; in addition, if gabapentin has an influence on mood, the secondary outcomes which did show superiority of gabapentin may be due to its effect on mood
- Most patients did not have pain relief with gabapentin; it is possible that neuropathic pain due to trauma is less responsive to gabapentin than is postherpetic neuralgia (PHN) and diabetic neuropathy (DM)
- The placebo response during the first 5 weeks of treatment was better than the placebo response during the second 5 weeks, when it was being taken by patients who had been taking gabapentin during the first 5 weeks; this points to a period effect

Comments:

- The discrepancy between the pain VAS analyzed with ANCOVA and pain improvement on other scales may have been due to the numerical distribution of the pain scores; if they were far from normally distributed, the distribution assumptions of ANCOVA could have been violated enough to obscure a treatment difference
- Although a minority of patients had good pain relief with gabapentin, it is not clear that it is greatly inferior to its effectiveness in PHN and DM, where a large proportion of patients are also not affected by treatment
- The period effect applies equally to both gabapentin and placebo, and should not create bias in the treatment effect, but it does suggest that the condition being treated may not be as stable as expected

Assessment: Adequate for evidence that gabapentin may be of moderate benefit for post-traumatic neuropathic pain